under 35 U.S.C. § 103(a), contending that the claims are anticipated by or, in the alternative, are obvious in view of Wiles et al. Specifically, the Examiner states that the arguments presented in the Amendment and Response filed July 29, 1997, do not appear to distinguish the cells disclosed by Wiles et al. as different from those claimed in the present invention. The Examiner alleges that the cell population disclosed by Wiles et al. is identical to the claimed cell population, and further contends that even if the two populations were different, that it would have been obvious to one of ordinary skill in the art to produce the claimed population. The Examiner further states that the U.S. Patent Office is not equipped to conduct experimentation to determine whether Applicants' populations differ, and therefore the burden of establishing non-obviousness by objective evidence is shifted to Applicants.

Applicants traverse the Examiner's rejection of Claims 27-35, 37-56, 58-59 and 108 under U.S.C. § 102(b) or § 103(a), and reassert that Wiles et al. do not teach or suggest the claimed embryonic blast cell population. Applicants respectfully submit that the comparative data alluded to by the Examiner in the Office Action is already set forth in the specification and in the Wiles et al. reference. The points of distinction are noted in the previous response filed on July 29, 1997, and are summarized for the Examiner below.

First, with regard to the Examiner's rejection under § 102(b), based on the contention that the Wiles et al. teach the claimed embryonic blast cell population, Applicants provide the following comments in traverse of this statement.

1.0 For the Examiner's reference during the following discussion, a direct comparison of the cell population disclosed by Wiles et al. versus the claimed cell population is set forth in the table below. This information can be readily obtained from the specification (Example 5) and from the Wiles et al. publication (page 261, col. 2, middle section; page 262, col. 2, 3rd & 4th full paragraph).

Lineages Identified In The Cell Populations Being Compared	Wiles Et Al. Embryoid Bodies	Claimed Embryonic Blast Cell Population (Derived From Embryoid Bodies)
Primitive Erythroid Lineage Precursors	No	Yes
Definitive Erythroid Lineage Precursors	No	Yes
Myeloid Lineage Precursors	No	Yes
Clonal Analysis to Verify Derivation from Single Cell	No	Yes

2.0 Wiles et al. do not teach the claimed cell population, because Wiles et al. do not teach or suggest an embryonic blast cell population (a population derived from an embryoid body (EB) population) that has the potential to develop into cells of (1) the primitive erythroid lineage; and

(2) the definitive erythroid, myeloid and endothelial lineages. Instead, Wiles et al. culture embryonic stem (ES) cells to form embryoid bodies (EB) under different conditions than the present inventors in order to show that embryoid bodies differentiate into established hematopoietic cells (i.e., established erythroid, macrophage, neutrophil and mast cell). Wiles et al. do not identify or isolate any hematopoietic precursor populations from the embryoid bodies and would not have isolated such populations because, under the culture conditions of Wiles et al., the cells committed to a cellular lineage early in the tissue culture process (i.e., the EB cell population lost pluripotency). Indeed, the first cell population to be identified in the EB cell population of Wiles et al. after the beginning of culture of the ES cells is the established erythroid lineage at 7-8 days (i.e., a later, different cell than an erythroid precursor), followed by the established macrophage lineage at 12-18 days (see page 261, col 2, second section).

In contrast, the present inventors are the first to identify and the first to isolate (i.e., to maintain the cell population in culture at a stage of pluripotency) a cell population which comprises a common, primordial, pluripotential hematopoietic precursor population, such precursor population being distinguished from any other embryonic blast cell population (or embryoid body population)

identified in the art, because it has the potential to generate cells of the primitive erythroid lineage, all other hematopoietic lineages (including the definitive erythroid, and myeloid lineages), and endothelial lineages (see specification, Example 5). This is a significant discovery, since this precursor is the earliest hematopoietic precursor to have been identified at the time of the present invention.

3.0 Prior to the present invention, it was not known that the primitive erythroid lineage derives from a single precursor that also can generate cells of other hematopoietic lineages. This is an unexpected result. The present inventors are the first to demonstrate the existence of such a precursor. Wiles et al. do not appreciate that such a precursor exists, and therefore, could not anticipate or suggest the identification or isolation of such a precursor.

Second, with regard to the Examiner's allegation that even if the cell populations are different, it would have been obvious to one of ordinary skill in the art to derive the populations, Applicants provide the following comments in traverse of this statement.

1.0 The culture conditions of Wiles et al. fail to isolate or identify a single pluripotent precursor population which is capable of differentiating into primitive erythroid cells and many other hematopoietic and endothelial lineages.

This is not insignificant, contrary to the Examiner's apparent contention that culture conditions are easily modified to obtain a desired population. If the Examiner's contention were true, multipotential precursor populations would have been identified and isolated long before the present invention. Indeed, within the art of hematopoiesis, the ability to identify and maintain a pluripotent precursor in culture is a significant achievement and is not merely a routine modification of known culture conditions (see Wiles et al. page 266, col. 2, 2nd full paragraph).

2.0 Moreover, to isolate a very early precursor population which was previously not known to exist, as the present inventors have done, is both unexpected and provides significant advantages to investigators interested in, for example, repopulating the hematopoietic cells of irradiated recipients. As discussed in the previous response, on page 266, Wiles et al. acknowledge that the repopulating hematopoietic stem cells and lymphoid precursors have not been identified or isolated, and that the identification of such cells may be difficult (column 2, second full paragraph). Clearly, Wiles et al. did not even know whether it would be feasible to isolate early precursors, which provides further evidence that the claimed invention is not made obvious by Wiles et al.

3.0 Prior to the present invention, it was known to culture embryonic stem (ES) cells to form embryoid bodies and to observe various cell lineages that grow from these cells as a result of changing culture conditions. This was the experimental design of Wiles et al. In studies such as Wiles et al., one might assume that hematopoietic precursors developed at some stage of EB development, because several lineages (i.e., endpoints) grew out of these structures, but the precursors themselves are neither identified nor isolated, and thus the relationship between precursors is also not discovered.

The present inventors developed culture conditions that promoted the isolation and growth of the claimed cell population in culture, and thereby demonstrated the existence of the claimed primordial hematopoietic cell. As discussed in the previous response, the specification goes to great lengths to point out the conditions which allowed the present inventors to identify and maintain in culture the claimed embryonic blast cell populations. Applicants submit that if it were obvious to modify the teachings of Wiles et al. to arrive at the claimed invention, then many investigators would have done so prior to the present invention.

In view of the foregoing discussion, Applicants submit that a comparison of the Wiles et al. reference with the present

specification establishes that Wiles et al. do not teach or suggest Applicants' claimed population. Therefore, the cited reference fails to teach every element of the claimed invention. Moreover, given the lack of knowledge regarding the identification of primordial hematopoietic precursors and techniques by which to identify such cells, together with the unexpected identification of the claimed totipotent precursor population by the present inventors, the Examiner has failed to establish a *prima facie* case of obviousness. Applicants respectfully request that the Examiner withdraw the rejection of Claims 27-35, 37-56, 58-59 and 108 under 35 U.S.C. § 102(b) and under § 103(a).

Applicants submit that all pending claims are in condition for allowance and request the Examiner's favorable consideration and allowance thereof. Applicants have tried to respond to all issues raised by the Examiner in the November 12, 1997, final office action. Applicants' attorney requests the courtesy of a telephone call from the Examiner in the event any of the claims are not considered to be in a condition for allowance.

Respectfully submitted,

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